REMARKS

The specification has been amended to capitalize trademarks and remove reference to embedded hyperlinks.

Applicants have cancelled Claims 8, 10, 15 and 16 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 1-7, 9, 11-12, and 14 to remove reference to the Figures. Claims 1-5 have been amended to add the limitation that the claimed nucleic acids are more highly expressed in normal lung tissue compared to lung tumor, or encode a polypeptide that is more highly expressed in normal lung tissue compared to lung tumor. Claims 1-7, and 9 have been amended to add the language "having the amino acid sequence of amino acids 34-321 of" SEQ ID NO:10. Claims 1-6, and 9 have been amended to specify the amino acids of the extracellular domains. Claim 14 has been amended to delete elements (a)-(d), to specify the conditions under which hybridization occurs, and to specify that the claimed nucleic acid be at least about 1000 nucleotides in length.

Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendment to Claims 1-5 regarding differential expression in normal lung and lung tumor can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification. Support for the amendment to Claims 1-7, and 9 regarding amino acids 34-321 can be found, for example, in paragraph [0196]. Support for the amendment to Claims 1-6, and 9 regarding the extracellular domains can be found, for example, in Figure 10. Support for the amendment to Claim 14 can be found, for example, in the definition of stringent conditions in paragraph [0227] of the specification and paragraph [0012].

Claims 1-7, 9, 11-14 and 17-20 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed September 8, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Specification

The disclosure was objected to by the PTO as containing embedded hyperlinks and/or other form of browser-executable code. The specification has been amended to remove reference to embedded hyperlinks. The specification has been further amended to indicate trademarks by capitalizing the trademarks and providing generic terminology.

As an initial matter Applicants wish to point out that amino acid 34 of SEQ ID NO: 10 is the initiator methionine, and amino acids 1-33 are not part of the PRO874 polypeptide. The full-length PRO874 polypeptide consists of amino acids 34-321 of SEQ ID NO: 10. In addition, the start codon of SEQ ID NO: 9 is the ATG beginning at nucleotide 100 of SEQ ID NO: 9. The amendments to the Claims to reflect this do not add new matter, as the specification indicates at paragraph [0196] that methionine 34 can be the starting amino acid of PRO874.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO has rejected Claims 1-10 and 14-20 as lacking enablement. According to the PTO, the specification does not enable any person skilled in the art to use the invention commensurate in scope with the claims. The PTO states that the only use for degenerate polynucleotides or variant degenerate PRO polynucleotides is the production of the encoded polypeptide or the production of variant PRO polypeptides, respectively. The PTO notes that SEQ ID NO: 10 does not begin with an initiator methionine and therefore less than a full-length protein is disclosed. The PTO states that if the specification does not disclose the full-length or mature native PRO polypeptide and does not disclose the activity exhibited by the full-length or mature native PRO polypeptide, and if the claims are not limited by any functional limitation, then the specification has not enabled the screening of any variants for activity exhibited by the full-length or mature native sequence.

In addition, the PTO states that although the data of Example 18 discloses that SEQ ID NO: 9 is more highly expressed in normal lung than as compared to lung tumor, the specification

provides no information regarding the level of expression, activity, or role in cancer of PRO874. Relying on Allman *et al.* (Blood, 87(12):5257-68 (1996)), the PTO argues that differential tissue nucleic acid expression is not always correlated with protein levels. The PTO concludes that therefore, the [higher] expression of SEQ ID NO: 9 in normal lung compared to lung tumor does not provide a readily apparent use for the PRO polypeptide.

Applicants respectfully traverse.

Applicants acknowledge that the PTO has not rejected Claims 11-13 as lacking enablement. However, Applicants respectfully disagree with the PTO's statement that the remaining claimed nucleic acids lack utility. Applicants submit that because the nucleic acid of SEQ ID NO: 9 is overexpressed in certain cancers, the protein encoded by SEQ ID NO: 9 also has utility in diagnosing cancer and further characterizing tissue samples. Thus, degenerate and variant nucleic acids which encode the polypeptide of SEQ ID NO: 10 have utility and are enabled as well.

Applicants have established that the Gene Encoding the PRO874 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful and Enabled as a Diagnostic Tool

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to enable use of the claimed nucleic acids as diagnostic tools, as described in the specification, for example, at paragraph [0336].

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). As Mr.

Grimaldi states, "If a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor." (Paragraph 7, emphasis added).

The data presented in Example 18 show that the gene encoding PRO874 is more highly expressed in normal lung tissue compared to lung tumor. As the Grimaldi declaration indicates, the disclosed gene and its corresponding polypeptide and antibodies are therefore useful as diagnostic tools. No additional research into how PRO874 is related to cancer is required to use the disclosed polynucleotides, polypeptides and antibodies to distinguish tumor cells from their normal tissue counterparts.

Because the PRO874 gene is underexpressed in lung tumor, nucleic acids which hybridize to the PRO874 gene can be used to compare expression levels of this sequence in normal tissue and tissue samples suspected of being cancerous. Applicants have amended Claim 14 to claim nucleotides which hybridize under the specified stringent conditions to the nucleic acid sequence of SEQ ID NO:9, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:9, or the full-length coding sequence of the cDNA deposited under ATCC accession number 209922. Nucleic acids such as these which hybridize to the PRO874 gene have are enabled as diagnostic probes, since techniques for measuring gene expression of a disclosed sequences are well-known in the art.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO argues the specification provides no information regarding the level of expression, activity, or role in cancer of PRO874. Relying on Allman *et al.* (Blood, 87(12):5257-68 (1996)), the PTO argues that differential tissue nucleic acid expression is not always correlated with protein levels. The PTO focuses on the finding reported by Allman *et al.* that germinal center B cells express dramatically more BCL-6 protein than resting B cells, despite similar BCL-6 mRNA levels in the two cell populations. Office Action at 7. The PTO concludes that therefore, the [higher] expression of SEQ ID NO: 9 in normal lung compared to lung tumor does not provide a readily apparent use for the PRO polypeptide.

The standard for establishing a use for a claimed invention is not absolute certainty, and thus a *necessary* correlation between mRNA levels and protein levels is not required.

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted).

As detailed below, Applicants assert that it is well-established in the art that in general, the level of protein is positively correlated to the level of mRNA. In spite of the fact that Allman *et al.* report a single contrary example, the cited reference actually supports Applicants' assertion.

In the discussion of their finding that mRNA and protein levels were not correlated, Allman *et al.* refer to the discovery as a "striking dichotomy." Allman *et al.* at 5265, second column, last paragraph. They also state that "an *unanticipated* finding was that the higher BCL-6 protein levels...could not be fully accounted for by increased mRNA expression." Allman *et al.* at 5267, column 1, carryover paragraph (emphasis added). Both of these statements indicate that normally, protein expression is correlated to mRNA levels, and their findings to the contrary were unexpected for that reason.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted use. Thus, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between protein level and mRNA levels. As the discussion in Allman indicates, the working hypothesis among those skilled in the art is that there is a direct correlation between protein levels and mRNA levels.

In support of this assertion, Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased

polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002) submitted herewith as Exhibit 4). Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Molecular Biology of the Cell at 302, emphasis added. Similarly, figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Molecular Biology of the Cell at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Molecular Biology of the Cell at 379.

Together, the declarations of Grimaldi and Polakis, the accompanying references, the excerpts from the Molecular Biology of the Cell, and the statements from Allman *et al.* all

establish that the accepted understanding in the art is that there is a correlation between gene expression and the level of the encoded protein. Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is expressed at a higher level in normal lung tissue compared to lung tumor, the PRO874 polypeptide will also be expressed at a higher level in normal lung tissue compared to lung tumor.

One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue could be uses as a diagnostic tool, for example, to generate antibodies. It follows that a nucleic acid which encodes a polypeptide that has use as a diagnostic tool, would likewise have such a use. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would know how to use the PRO874 polypeptide, and the nucleic acids which encode it, as a cancer diagnostic tool.

Applicants submit that they have therefore established two separate bases for using the claimed nucleic acids. The first argument is based on the differential expression of the PRO874 gene in normal lung tissue compared to lung tumor. Nucleic acids that can be used to detect the expression of the PRO874 gene are thus enabled. The second argument is based on the use of the PRO874 polypeptides as diagnostic tools, given that it is well-established in the art that there is a correlation between gene expression and protein expression. Because it is more likely than not that the PRO874 polypeptide is differentially expressed in lung cancer, the PRO874 polypeptides have an enabled use, e.g. generating antibodies. Likewise, nucleic acids encoding these polypeptides also have an enabled use. That includes degenerate nucleic acids as well as homologous nucleic acids which can be used to generate antibodies to PRO874.

The Claimed Nucleic Acids would be Enabled for Use as a Diagnostic Tool even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO874, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** be enabled for use as a diagnostic tool.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 5), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 6). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still be useful, as would the nucleic acid which encodes it. Thus, Applicants have demonstrated another basis for enablement of the claimed nucleic acids.

Conclusion

Example 18 shows that the PRO874 gene is more highly expressed in normal lung tissue compared to lung tumor. Therefore, nucleic acids which can detect the level of PRO874 gene expression are enabled as diagnostic tools. Because protein levels are generally correlated with gene expression, it is more likely than not that the PRO874 polypeptide is also more highly expressed in normal lung tissue compared to lung tumor. Thus, nucleic acids which can be used to make antibodies to detect the level of PRO874 polypeptide in tissue are enabled as diagnostic

tools. Measurement of PRO 874 polypeptide levels is useful even if there is no correlation between gene expression and protein expression, since this information in conjunction with gene expression data can be used to further classify the kind of tumor tissue being studied. Thus, those of skill in the art would recognize and understand how to use the claimed nucleic acids as diagnostic tools. Hence, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejected Claims 1-5 and 14-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of

his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The subject matter of the pending claims concerns nucleic acids having a specified sequence identity with the disclosed polynucleotide sequence of SEQ ID NO: 9, or encoding a polypeptide with the specified polypeptide sequence of SEQ ID NO: 10, and as amended, with the functional recitation: "wherein said isolated nucleic acid is more highly expressed in normal lung tissue compared to lung tumor, or wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in normal lung tissue compared to lung tumor". Other claims relate to nucleic acids which hybridize to nucleic acids of SEQ ID NO: 9 under the stringent conditions which have now been specified in Claim 14.

Based on the detailed description of the cloning and expression of PRO874 in the specification, the description of the gene amplification assay, the actual reduction to practice of sequences SEQ ID NOs: 9 and 10, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the subject matter of the pending claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6, 8, 10, and 14-20 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the recitation of "signal peptide," "the extracellular domain," and "stringent conditions."

Applicants have amended the claims to eliminate any recitation of a signal peptide, and to specify the amino acids of the extracellular domain. Claims 15 and 16 have been canceled. Applicants have amended Claim 14 to specify the stringent conditions under which hybridization is assessed. In light of these amendments, Applicants request that the PTO withdraw the indefiniteness rejections under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(e) – Anticipation

The PTO rejects Claims 14-16 as anticipated under 35 U.S.C. § 102(e) by Edwards, U.S. Patent No. 6,312,922, which was published on October 1, 1999. The PTO states that Edwards discloses an isolated nucleic acid molecule (SEQ ID NO: 141) that has a Best Local Similarity of 98.2% to SEQ ID NO: 9. The PTO states that Edwards first disclosed the molecule in U.S. Application No. 60/081,563. The PTO argues that in view of the high percent homology, the complement of the Edward's nucleic acid would hybridize to SEQ ID NO: 9 even under stringent conditions.

Applicants have canceled claims 15 and 16. Claim 14 has been amended to include the limitation "wherein said isolated nucleic acid is at least about 1000 nucleotides in length." As SEQ ID NO: 141 of the Edwards patent is only 891 nucleotides long, the Edwards patent does not disclose each element of the pending claim. Thus, Applicants respectfully submit that the cited reference does not anticipate Claim 14 as amended, and request that the rejection under 35 USC §102(e) be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Dec. 7, 2004

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